

Cerebral Dysfunction in Rheumatic Chorea: A Recent Approach to the Etiology of Pediatric OCD

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Abstract

The aim of this work was to study the regional cerebral blood flow (r-CBF) and the neuropsychological correlates in children with rheumatic chorea in an attempt to clarify the cerebral dysfunction in rheumatic chorea and to varify the possible co-morbidity of rheumatic chorea with obsessive compulsive symptoms (OCS). Twenty-eight children with rheumatic chorea were included in this study, 13 were studied during the course of their illness while 15 were considered full recovered at the time of the study. All children were subjected to physical examination, neuropsychological testing, semi-structured psychiatric interview and (r-CBF) using ^{99m}Tc -HMPAO SPECT. Fifteen children were selected as a control group with matched age, sex and level of education. The results showed that 60.7% of patients had OCS. Neuropsychological tests revealed that patients scored significantly less than the control group in verbal fluency, picture arrangement and block design. Cerebral hypoperfusion was found in 92.3% of children who had current rheumatic chorea and in 86.6% of children who improved completely. Positive correlation was found between impairment of neuropsychological tests and decreased cerebral blood flow in certain areas of the brain including the basal ganglia. This study concludes that rheumatic chorea is associated with changes in clinical, neuropsychological and r-CBF suggestive of short and long term cerebral dysfunction and that rheumatic chorea could nerve as a medical model for OCD.

Introduction

Chorea is a hyperkinetic, rapid, unsustained irregular, purposeless and nonpatterned movement (Painter and Bergman, 1994).

Syndenham's chorea "rheumatic chorea", is the most common acquired chorea of childhood and is the sole neurologic manifestation of rheumatic fever. Moreover, rheumatic chorea is the only symptom of rheumatic fever; it is for this reason the World Health Organization suggested that this symptom alone is adequate to satisfy the diagnosis (Haslam, 1992).

The pathophysiology of rheumatic chorea is thought to involve an autoimmune response to neurons within the central nervous system. Antibodies produced in response to

group A-B hemolytic streptococci (GABHS) mistake the child's neuronal cells as foreign and initiate an inflammatory reaction. The basal ganglia region seems to be particularly vulnerable to these antineuronal antibodies (Swedo et al., 1994).

The role of brain SPECT in the diagnosis of rheumatic chorea have been studied by Heye et al., (1993) who performed brain SPECT using ^{99m}Tc -HMPAO in a study of patients with rheumatic chorea, they reported marked brain hypoperfusion in the region of the left basal general.

On the other hand, Hill et al., (1994) on their study of rheumatic chorea patients

using 99m TC-HMPAO SPECT found normal brain perfusion pattern.

Rheumatic chorea is one of childhood movement disorder with the potential to contribute to our understanding of pediatric OCD (Swedo and Leonard, 1994). In addition to the neurological manifestations, emotional lability and psychiatric symptomatology, such as separation anxiety, hyperactive and/or OCD are also prominent features of this semiacute illness (Swedo et al., 1993).

Swedo et al., (1993) found that children with rheumatic chorea exhibited increased emotional lability, obsessive-compulsive symptomatology and decreased attentiveness shortly before the onset of their choreiform movements. In addition, they mentioned that these acute Obsessive-Compulsive Symptoms found in children with rheumatic chorea are identical with those of children with obsessive-compulsive disorder, and they suggested that rheumatic chorea may serve as a medical model for obsessive-compulsive disorder, which is thought to be related to dysfunction of basal ganglia-Limbic frontal circuit.

Moreover, obsessive-compulsive symptoms arising or exacerbating in the context of (GABHS) which has been given the eponym "Pediatric Autoimmune Neuropsychiatric Disorders Associated with streptococcal infections" or PANDAs- may define a singular subgroup with pediatric-onset OCD (Allen et al., 1995).

In fact, Swedo and Colleagues have theorized that OCD in the context of rheumatic chorea may provide a medical model for the etiopathogenesis of OCD and tic disorders (Sweds et al., 1993).

Until recently, it was beyond any expectations that a subgroup of OCD patients may exist and could be treated with antibiotics (Okasha, 1998). A homogenous group of OCD patients were described by Swedo et al., (1998) in whom symptom exacerbation was triggered by (GABHS) infections such a subgroup will allow for the testing of models of pathogenesis, as well as the development of novel treatment and prevention strategies.

The main objectives of this work was to study the regional cerebral blood flow (r-CBF) and the neuropsychological correlates in patients with rheumatic chorea in order to identify the role of cerebral dysfunction in rheumatic chorea and to clarify the possible comorbidity between rheumatic chorea and obsessive-compulsive symptoms (OCS).

Subjects and Methods

This study comprised 28 patients with rheumatic chorea and they were divided into two groups.

Group (A) consisted of 13 patients (9 girls and 4 boys) with a mean age of (9 ± 2 years), they were studied during their first attack of rheumatic chorea, while group (B) included 15 patients (9 girls and 6 boys) with a mean age of (9.7 ± 1.4 years), each had a single attack of rheumatic chorea and were considered completely recovered.. The mean duration of recovery was (1.33 ± 0.36 years) before the study.

Fifteen children of matched age and sex were selected as a control group. The study was carried out in the Children Hospital and the Institute of Psychiatry, Ain Shams University Hospitals, Cairo, Egypt.

An informed parental consent for joining this study was obtained from each subject

prior to enrollment. All patients and control groups were subjected to: (i) full history taking with special emphasis on the illness (ii) clinical examination (iii) neuropsychological test using the following: Subscales from Wechsler Intelligence Scale for children; similarities, digit span; picture completion, block design; picture arrangement and verbal fluency. (iv) detection of OCS using semi-structured Clinical Psychiatric Interview based on the ICD-10 (Sayed et al., 1994), with special emphasis on obsessive-compulsive symptoms based on Yale-Brown Obsessive-Compulsive Scale (Y-OCS). (v) laboratory tests including Erythrocyte Sedimentation Rate (ESR), C-reactive protein and antistreptolysin O-titre (vi) functional brain imaging using ^{99m}Tc -HMPAO SPECT, but for ethical reason only 5 children from the control group were subjected to ^{99m}Tc -HMPAO SPECT.

The data collected were introduced to a personal computer and the following statistical procedures have been done the mean and standard deviation, student's t-test and chi square test.

Results

The results of this work will be clarified in the following items:

1- Patients characteristics

Thirteen patients in group (A) were diagnosed as having rheumatic chorea based on the history and clinical examination, their sex distribution, male to female ratio was, 1:2.3 and their mean age was (9 ± 2) years. The mean duration of the illness was (7.4 ± 1.1) weeks.

The total number of patients in group (B) were 15, with a mean age of 9.7 ± 0.36 and male to female ratio was 1:1.5. Patients in

this group were free from any choreic movements and were considered to be fully recovered 1.33 ± 0.36 years before the time of the study.

2- Comparison between group A,B and the control group:

a- Laboratory investigations:

The results of laboratory tests found that patients in group (A) had a significantly higher ESR and ASOT than those of (B) group and control group ($P < 0.05$).

b- Neuropsychological assessment:

It was found that patients in both group A and B scored significantly less than control in verbal fluency and picture arrangements tests. While patients in group (A) experienced significantly less than the control in Block Design Test. On the other hand group (B) patients scored significantly less than the control in Digits Span Test (Table 1).

Table (2) shows the distribution of obsessive-compulsive symptoms among group (A), (B) and control group. It was found that patients belonging to both groups had significantly more obsessive-compulsive symptoms (OCS) than the control group 61.5% and 60% respectively ($P < 0.05$), mean while the difference between group (A) and (B) was statistically insignificant ($P > 0.05$).

Compulsive symptoms were found to be significantly more than obsessive among group (A) and (B) ($P < 0.05$).

The most common compulsions found in their order of frequency were washing, checking and repeating. On the other hand, the only type of obsession found was fear of contamination.

C- Brain SPECT studies

Study of regional cerebral blood flow (r-CBF) using ^{99m}Tc HMPAO-SPECT found that all the controls had normal cerebral perfusion (Figure - 1).

Cerebral hypoperfusion was found in 12 patients (92.3%) belonging to group (A) and 13 patients (86.6%) belonging to group (B). Table (3) shows the mean values of tracer uptake by different lobes among patients of group (A), (B) and the control group. When compared to controls a significant reduction was found in the mean tracer uptake by the right basal ganglia, frontal, parietal, occipital and left temporal lobes in patients in group (A); and by the basal ganglia, frontal, parietal, and left occipital lobes in patients belonging to group (B), (Figure 2 and 3).

Frontal lobe hypoperfusion was significantly found in patients manifesting obsessive compulsive symptoms (OCS) in both group (A) and (B) when compared to those patients with no (OCS) ($P < 0.05$). Moreover, a significant involvement of the parietal lobe was found in patients belonging to group (B) manifesting (OCS)

compared to those patients with no (OCS) (Table 4). On the other hand no significant difference was found between patients who had obsession and those who had compulsions in both group (A) and (B), ($P > 0.05$), regarding the (r-CBF) and neuropsychological testing. (Table 4).

The correlation between the changes in neuropsychological test and the r-CBF was studied in this work. There was a positive correlation between verbal fluency test score and decreased tracer uptake (hypoperfusion) in the left frontal lobe among patients in group (A) and right superior frontal lobe among patients in group (B). Moreover, a positive correlation was found between digit span test score and decreased tracer uptake by the left inferior frontal lobe among group (A) and (B). As regards picture arrangement test, its score was positively correlated to the decreased tracer uptake by left superior frontal lobe in patients of group (A) and the left parietal lobe among patients in group (B).

Table (1):

The comparison between group A and B and the control in neuropsychological tests

Variable	Group (A) n=13	Group (B) n=15	Control n=15	A # C	B # C	A # B
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	P	P	P
Similarities	10.5 $\pm$ 1.9	10.6 $\pm$ 1.8	11.8 $\pm$ 2.5	> 0.05	> 0.05	> 0.05
Digit span	8.8 $\pm$ 2.3	8.1 $\pm$ 2.4	9.4 $\pm$ 0.2	> 0.05	< 0.05	> 0.05
Picture completion	8.2 $\pm$ 2.6	10.1 $\pm$ 3.9	8.9 $\pm$ 1.5	> 0.05	> 0.05	> 0.05
Picture arrangement	5.2 $\pm$ 1.2	5.5 $\pm$ 3.0	8.5 $\pm$ 1.4	< 0.05	< 0.05	> 0.05
Block design	6.2 $\pm$ 1.9	7.9 $\pm$ 2.3	8.2 $\pm$ 0.6	< 0.05	> 0.05	< 0.05
Verbal fluency	8.5 $\pm$ 3.2	13.1 $\pm$ 8.9	20.5 $\pm$ 3.4	< 0.05	< 0.05	> 0.05

$P > 0.05$ = Non significant

$P < 0.05$ = significant

Table (2): The distribution of obsessive compulsive symptoms (OCS) among group A and B and the control

Variable	group (A) n=13		Group (B) n=15		Control n=15	P - value		
	n	%	n	%		A # C	B # C	A # B
Obsession	1	7.7%	3	20%	0	> 0.05	> 0.05	> 0.05
Compulsion	5	38.5%	4	26.7%	0	< 0.05	< 0.05	> 0.05
Mixed	2	15.4%	2	13.3%	0	> 0.05	> 0.05	> 0.05
Total	8	61.5%	9	60%	0	< 0.05	< 0.05	> 0.05

P>0.05 = Non significant

P<0.05= significant

Table (3): Statistical comparison of mean value of tracer uptake by different lobes between group A, B and C

Variable	Group (A) n=13	Group (B) n=15	Control n=15	A # C P	B # C P	A # B P
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD			
Rt. Superior	0.90 $\pm$ 0.08	0.90 $\pm$ 0.11	1.0 $\pm$ 0.04	<0.001 Sig.	<0.001 Sig.	>0.05 NS
Lt. Superior frontal	0.85 $\pm$ 0.25	0.85 $\pm$ 0.09	1.02 $\pm$ 0.02	<0.05 Sig.	<0.001 Sig.	>0.05 NS
Rt. Inferior frontal	0.91 $\pm$ 0.08	0.91 $\pm$ 0.1	1.0 $\pm$ 0.02	<0.001 Sig.	<0.01 Sig.	>0.05 NS
Lt. Inferior frontal	0.90 $\pm$ 0.10	0.89 $\pm$ 0.07	1.0 $\pm$ 0.05	<0.01 Sig.	<0.001 Sig.	> 0.05 NS
Rt. Basal ganglia	0.84 $\pm$ 0.11	0.86 $\pm$ 0.11	0.96 $\pm$ 0.09	<0.05 Sig.	<0.05 Sig.	>0.05 NS
Lt. Basal ganglia	0.85 $\pm$ 0.10	0.82 $\pm$ 0.08	0.93 $\pm$ 0.08	>0.05 NS	<0.05 Sig.	>0.05 NS
Rt. Temporal	0.92 $\pm$ 0.13	0.90 $\pm$ 0.09	0.94 $\pm$ 0.04	>0.05 NS	>0.05 NS	> 0.05 NS
Lt. Temporal	0.85 $\pm$ 0.08	0.88 $\pm$ 0.09	0.91 $\pm$ 0.02	<0.05 Sig.	>0.05 NS	>0.05 NS
Rt. Occipital	0.90 $\pm$ 0.11	0.94 $\pm$ 0.13	0.97 $\pm$ 0.06	>0.05 NS	>0.05 NS	>0.05 NS
Lt. Occipital	0.89 $\pm$ 0.10	0.94 $\pm$ 0.10	1.0 $\pm$ 0.04	<0.01 Sig.	<0.05 Sig.	>0.05 NS
Rt. Parietal	0.88 $\pm$ 0.08	0.89 $\pm$ 0.11	0.95 $\pm$ 0.03	<0.05 Sig.	<0.05 Sig.	>0.05 NS
Lt. Parietal	0.87 $\pm$ 0.10	0.85 $\pm$ 0.11	0.95 $\pm$ 0.03	<0.05 Sig.	<0.01 Sig.	>0.05 NS

Table (4) : Extent of cerebral blood flow changes in patients with OCS versus those with no OCS in both group A & B

Area affected	Group A			Group B		
	Patients without OCS	Patients with OCS	P	Patients without OCS	Patients with OCS	P
	(N=5)	(N=8)		(N=6)	(N=9)	
Frontal lobe	0 (0%)	4 (50%)	<0.05 Sig.	0 (0%)	4 (44.4%)	10.05 Sig.
Basal ganglia	4 (80%)	8 (100%)	>0.05 NS	4 (66%)	8 (88.9%)	>0.05 NS
Temporal lobe	1 (20%)	3 (37.5%)	>0.05 NS	0 (0%)	1 (11.1%)	>0.05 NS
Occipital lobe	1 (20%)	2 (25%)	>0.05 NS	0 (0%)	0 (0%)	>0.05 NS
Parietal lobe	1 (20%)	4 (50%)	>0.05 NS	0 (0%)	4 (44.4%)	<0.05 Sig.

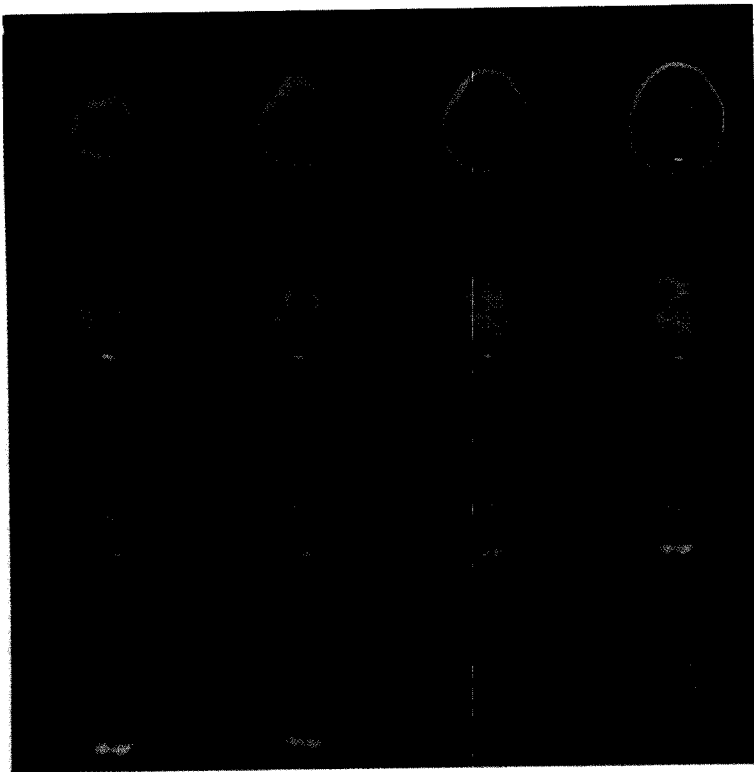


Fig (1)
Brain SPECT of control showing normal cerebral perfusion

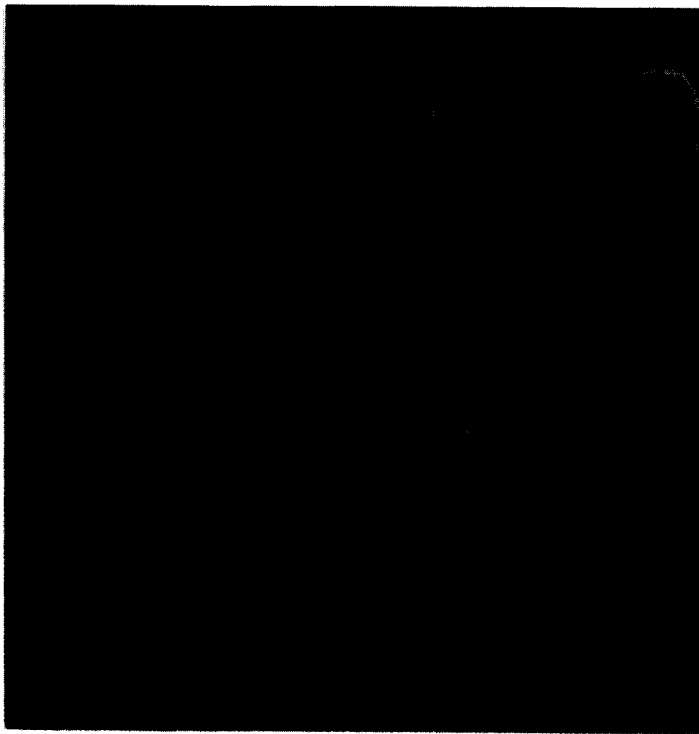


Fig (2)
Brain SPECT of a case with rheumatic chorea showing significant tracer hypoperfusion in both basal ganglia and in left temporo-parietal cortex.

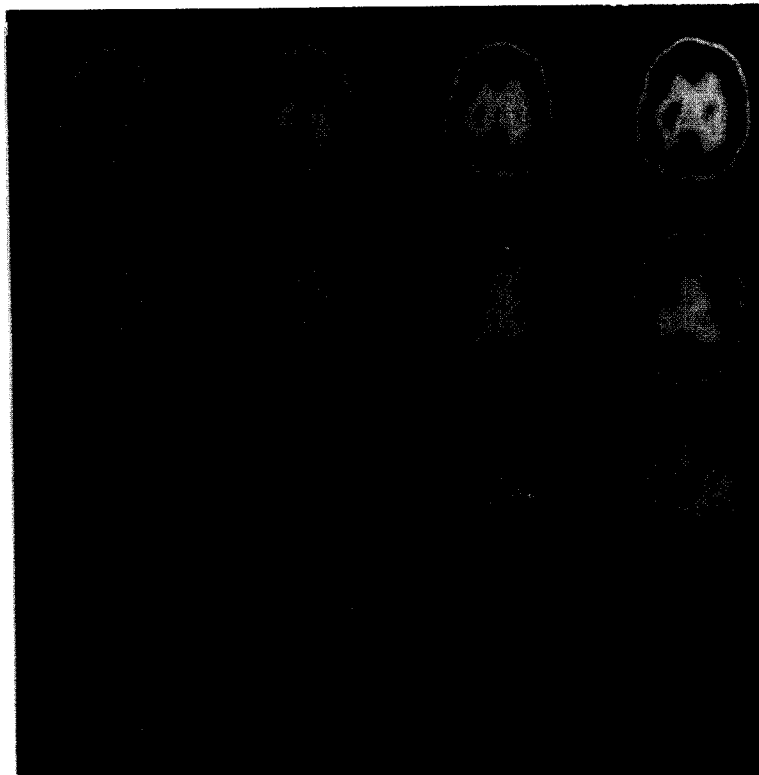


Fig. (3):
Brain SPECT of a case with past history of rheumatic chorea showing significant tracer hypoperfusion in left basal ganglia and left parietal cortex.

Discussion

This work was designed to clarify the role of cerebral dysfunction in rheumatic chorea in order to highlight the correlation between OCD and rheumatic chorea in an attempt to provide a recent model in the etiology of OCD.

In this work there was a significant increase in the mean ESR and ASO-titre of both group A and B than the control group, being significantly more in the acute cases. As patients in group (A) and (B) had evidences suggestive of streptococcal infection in the form of increasing ASO titre. However, Stollerman (1992) stated that chorea appears only after a relatively long latent period, as long as one to six months following the antecedent streptococcal infection and both the acute phase reactants and the streptococcal antibody titres may have returned to normal. Obsessive-compulsive symptoms have been found among both group (A) and (B), 61.5% and 60% respectively the difference between both groups was statistically insignificant while a significant difference was found between both groups and the control group. These obsessive-compulsive symptoms did not met with the OCD criteria. Moreover, compulsion was significantly more than obsessions in both group A & B while obsession was more in group (B) than in Group (A), 20% and 7.7% respectively, but the difference between both group was statistically insignificant.

Swedo et al., (1989) assessed 23 patients with rheumatic chorea and 14 patients with rheumatic fever but without chorea using Leyton Obsessional Inventory-Child version. They found significant increase in obsessiveness scores among patients with

rheumatic chorea compared with those without. In addition a prospective study by Swedo et al., (1993) of eleven children with rheumatic chorea had similar results. Nine of the eleven children exhibited obsessive-compulsive symptoms and four met diagnostic criteria for OCD. Both studies have found that obsessive compulsive symptoms began shortly before the onset of the chorea, peaked with movement disorder and decreased to undetectable by or before the disappearance of the choreic symptoms.

However, our work did not support these findings, as nine out of the fifteen patients with a history of single attack of rheumatic chorea, who were considered completely recovered (1.33 ± 0.36) years before, had obsessive-compulsive symptoms. This finding was supported by Denny (1994) who mentioned that OCD present in the absence of any rheumatic manifestation could be triggered by group (A) streptococcus infection. Moreover, in this work it was found that neuropsychological test includes verbal fluency, picture arrangement and block design test in patients belonging to group (A) were significantly less than the control group. Meanwhile group (B) patients, who were considered completely recovered from rheumatic chorea scored less than the control in verbal fluency, picture arrangement and digit span tests. These findings were not supported by Swedo et al., (1993) who found no significant difference in verbal fluency test between patients with syndrome's chorea and their matched control.

In addition, regional cerebral blood flow (r-CBF) using ^{99m}Tc -HMPAO SPECT found cerebral hypoperfusion in both group (A)

and (B), 92.3% and 86.6% respectively, significant reduction was found in the mean tracer uptake by the right basal ganglia, frontal, parietal, left temporal and occipital lobes in group (A) patients. While cerebral hypoperfusion was particularly found in the regions of the basal ganglia, frontal, parietal and left occipital lobes in patients belonging to group (B).

Using ^{99m}Tc HMPAO SPECT, Heye et al., (1993) in a single case study detected marked hypoperfusion in the region of the left basal ganglia. However, Hill et al., (1994), in a similar study, reported a normal perfusion pattern in a single case study with rheumatic chorea.

In an attempt to correlate between the results of neuropsychological evaluation and the functional brain imaging using ^{99m}Tc HMPAO SPECT, it was found that patients with rheumatic chorea (group A) and those with past history of rheumatic chorea (group B), who manifested OCS, had a significant involvement of the frontal lobe more than those who did not show OCS.

Swedo et al., (1993) speculated that the motoric symptoms in sydenham's chorea result primarily from basal ganglia dysfunction, while the concentration difficulties, emotional liability and obsessive compulsive symptoms are manifestation of both basal ganglia and other cortical dysfunctions.

Several studies have looked at the structural, functional and electrophysiological changes in obsessive compulsive disorder including [Machlin et al. (1991), Rubin et al., (1992), Perani et al., (1995), Okasha et al., (1996), Baxter et al., (1992) and Brody and Saxena, (1996)]. All the SPECT studies provided evidence of

frontal lobe hyperperfusion and basal ganglia hypoperfusion in OCD subjects. These studies partially supported the findings in this work. However, our findings pointed to frontal lobe hypoperfusions using HMPAO-SPECT for cerebral blood flow. This difference in the cerebral blood flow and the frontal perfusion could be explained by the disturbance in the blood-brain barrier caused by the streptococcal infection in cases of rheumatic chorea as HMPAO-uptake depends on the local functional properties and the permeability of the blood-brain barrier.

In view of this work one can conclude that rheumatic chorea previously known to be of good prognosis may result in both short and long-term brain dysfunction in the regions of basal ganglia and other cortical neuronal components. Moreover, rheumatic chorea manifests itself not only as motor symptoms but also as neuropsychological and functional brain disturbances. In addition, the significant presence of obsessive-compulsive symptoms during the acute and chronic phases of rheumatic chorea adds more to our understanding of OCD. Because the pathophysiology of rheumatic chorea is better defined than that of OCD, rheumatic chorea may serve as a medical model for some cases of childhood-onset OCD. As a result, children with a sudden onset or exacerbation of OCD or OCS and motoric symptoms in the context of an upper respiratory tract infection should be investigated for these antineuronal antibodies. Moreover, an empirical trial of antibiotic can be restricted to those cases. Finally, Holander and Benzaquen (1996) included Sydenham's chorea within the spectrum of obsessive-compulsive related disorders.

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الخلل المخى فى الداء الراقص:

نظرة حديثة لاسباب الوسواس القهرى فى الاطفال

الغرض من هذا البحث هو دراسة تدفق الدم الموضعى المخى و علاقتها بالتغيرات النفسية و العصبية فى مرضى الداء الراقص من الاطفال فى محاولة لتوضيح الخلل المخى بالداء الراقص و توضيح امكانية تلازم الداء الراقص مع اعراض الوسواس القهرى وتم فحص ٢٨ طفلا مصابين بالداء الراقص منهم ١٣ طفلا ما زالوا مرضى و ١٥ طفلا شفوا تماما اثناء هذه الدراسة.

تم فحص كل المرضى و تقييمهم اكلينيكيًا و نفسيًا و عصبيًا و بالفحص النفسى و بأستخدام (r-cbr)
عن طريق 99cm Tc-HMPAO SPECT .
تم اختيار ١٥ مريضًا كمجموعة تحكم مماثلة في السن و الجنس و نسبة التعليم و قد وضحت النتائج
٦٠,٧% من المرضى لديهم اعراض وسواس قهري .
كما ان نقص الدم المخى قد وجدت في ٩٢,٣% من الاطفال المصابين بالداء الراقص بينما النسبة
٨٦,٦% من الاطفال الذين اظهروا شفاء تام من هذا المرض .
كما اوضحت الدراسة ان هناك علاقة بين الخلل في الاختبارات العصبية و النفسية و نقص تدفق الدم
الموضعى المخى و خصوصا في اماكن معينة بالمخ مثل Basel Gang .
من هذه الدراسة نستنتج ان الداء الراقص مصحوب بتغيرات اكلينيكية و نفسية و تدفق الدم الموضعى
المخى و هذا ما يثبت وجود خلل مخى و ان الداء الراقص يمكن ان يستخدم كمثال طبى للوسواس
القهرى .